REMARKS

Reconsideration and allowance are respectfully requested.

Claims 7-10 and 13-14 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. Support may be found, inter alia, in original claims 9 and 10; on page 8, lines 2-6; on page 19, lines 18-24; from page 21, line 24, to page 22, line 24; from page 24, line 18, to page 25, line 8; and Fig. 1 of the specification.

Claims 1-6 were withdrawn from consideration by the Examiner. Therefore, they are canceled without prejudice or disclaimer to their future prosecution.

35 U.S.C. 112 – Definiteness

Claims 7-10 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse for the following reasons.

Method claims are revised to recite the preamble "determining whether a human subject is at increased risk for developing rheumatoid arthritis" (claim 7) or "determining whether a human subject has developed rheumatoid arthritis or has a likelihood of developing rheumatoid arthritis" (claims 9-10). At least one active step is recited in each method.

The abbreviation "RA" is recited in full as "rheumatoid arthritis" in the claims.

Claim 8 does not recite "DR3 gene promoter A regions" because this limitation is not required for patentability.

Claim 10 refers to "a human subject" (one source) and a healthy control (another source), which is used for comparison.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent

upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 7-10 were rejected under Section 112, first paragraph, because allegedly the specification does not reasonably provide enablement for "methods which determine the development of RA or likelihood of developing RA in any non-human subject, methods which determine the development of RA or likelihood of developing RA by assaying for the methylation status for any single CpG in the DR3 gene promoter or which analyze any region of the DR3 gene promoter, or methods which determine the development of RA or likelihood of developing RA by confirming by any means or methodology that the DR3 gene promoter obtained from synovial cells is strongly methylated." Applicants traverse because the teachings in their specification enable the skilled artisan to practice their invention as presently claimed.

Applicants found that methylation of CpG sequences in the promoter region of the DR3 gene was different when samples obtained from synovial tissues of RA (rheumatoid arthritis) patients and those obtained from synovial tissues of healthy subjects were compared. The claimed invention was based on this finding. Specifically, Applicants found that (i) the subject is already affected with RA or is more likely to develop RA in cases where three or more methylated CpG sequences exist in the C region (from base 374 to base 592 of SEQ ID NO: 1) of the DR3 promoter, and (ii) the subject is not affected with RA or is less likely to develop RA in cases where the CpG sequences in the C region (from base 374 to base 592 of SEQ ID NO: 1) of the DR3 promoter are not as methylated.

It was asserted in the Office Action there is no difference in the level of methylation in RA patients as compared to osteoarthritis (OA) patients. The present amendments, however, address this objection because they clarify that the claimed invention determines the likelihood (risk) for developing rheumatoid arthritis in a human subject. It was further asserted in the Office Action that association between the level of methyla-

tion in the DR3 promoter region and the development of rheumatoid arthritis is not supported by sufficient data. But Example (6) and Figs. 16(a)-16(b) of the present specification describe inhibition of the expression level of DR3 protein in synovial cells obtained from rheumatoid arthritis patients, where the DR3 promoter is highly methylated. These data make the crucial connection that the level of methylation in the DR3 promoter region is associated with the development of rheumatoid arthritis. Therefore, the skilled artisan would be taught by Applicants' specification that the level of methylation in the DR3 promoter region is clearly associated with the development of rheumatoid arthritis.

Applicants' invention is characterized not by any particular method of detecting the level of methylation, but in that it is possible to determine that a human subject has developed rheumatoid arthritis (or has the likelihood of developing rheumatoid arthritis) by detecting the level of methylation of a specific part of the DR3 promoter region obtained from specific cells. Any method of detecting methylation status may be used from those known to a skilled artisan. This is sufficiently described in Applicants' specification (see, for example, from page 25, line 19, to page 26, line 4, of the specification).

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 102 – Novelty

Claims 7-10 were rejected under Section 102(a) as allegedly anticipated by Takami et al. (Arthritis & Rheumatism, 50:S671, abstract 1796, Sep. 2004). Applicants traverse because the cited document is not prior art to the claims in this application.

Submitted herewith are verified English translations of the four Japanese priority applications. They show that the present claims are entitled to at least a priority date before the publication date of Takami.

Therefore, Applicants request withdrawal of the Section 102 rejection.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Gary R. Tanigawa/
Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100